

atrophy and intracellular accumulations of tau, TDP-43 or FUS protein. With the exception of a small number of familial forms the causes for FTLN are unknown. With our plasma proteomics approach we identified novel disease pathways that may open possibilities for treatment and diagnostics. **Methods:** We employed medium scale plasma proteomics, measuring more than 600 soluble cellular communication factors in plasma from control (n = 83) and FTLN (n = 92) patients with semantic dementia, as well as from FTLN patients with a familial Progranulin mutation (n = 24). We are using an antibody microarray based approach in combination with statistical and computational tools to identify altered pathways. **Results:** Our analysis revealed a deregulation of inflammatory markers, most prominently in the TNF-alpha and IL-1 pathways. We further confirmed an increase in TNF-alpha in the plasma of FTLN patients by ELISA. Currently we are in the process of analyzing the immune phenotype of FTLN patients and comparing it to healthy controls. **Conclusions:** Our results show evidence for a novel immune phenotype in FTLN patients with TDP-43 pathology. This opens up possibilities for a targeted anti-inflammatory therapy for this disease.

**FEATURED RESEARCH SESSIONS: F1-01
TACKLING OVERLAP OF NEUROPSYCHIATRIC SYMPTOMS IN
ALZHEIMER'S AND OTHER DEMENTIAS: TOWARD A UNIFIED
APPROACH TO EVALUATION AND TREATMENT**

**F1-01-01 EVIDENCE SUPPORTING USE OF NON-
PHARMACOLOGIC INTERVENTIONS FOR NPS:
WHERE DO WE GO FROM HERE?**

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Background: This presentation will describe the evidence supporting non-pharmacologic interventions for NPS, suggest potential treatment mechanisms, and provide recommendations for future research. A review of 26 meta-analyses published between 2001 to 2011 and summarizing 518 studies of nonpharmacologic treatments suggests limited but promising evidence. Two basic approaches have been tested: non-specific, generalized programs (e.g., therapeutic activity, caregiver training, environmental redesign) to prevent or minimize NPS overall; and problem-solving (4-D approach) to eliminate, reduce or prevent targeted behaviors. However, research on both approaches remains flecked by imprecision including lack of standardized implementation and poor characterization of treatments, inattention to mechanisms of action, poor characterization of samples concerning dementia-type and disease stage, and reliance on subjective outcome measures. Proposed is the need for multi-site, large scale clinical trials to test the most promising nonpharmacologic approaches and which better characterize and link interventions, samples and presenting NPS. Future research must also contend with harmonizing NPS measures for comparative purposes, specifying nonpharmacologic strategies by dementia-type and behavior cluster, determine start and stop rules for using nonpharmacologic approaches, and evaluate mechanisms for integrating this approach in standard care.

**F1-01-02 TACKLING OVERLAP OF NEUROPSYCHIATRIC
SYMPTOMS IN ALZHEIMER'S AND OTHER
DEMENTIAS: TOWARD A UNIFIED APPROACH TO
EVALUATION AND TREATMENT**

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Background: Neuropsychiatric symptoms (NPS), while nearly universal in AD, tend to occur in phenotypic clusters, which may reflect distinct pathophysiologies arising from specific underlying brain damage. Therefore, treatments targeting their specific cause(s) are required. For example, symptom clusters ("syndromes") characterized as affective, psychotic, agitated, apathetic, or reflecting sleep-wake cycle disorders have been proposed. Individual symptoms may co-occur in more than one syndrome at a given

time, and these relationships may differ across the MCI to severe AD spectrum. Adding to the complexity, many NPS are thought to be the short-term result of environmental provocations (reactive psychological states and behaviors) which partly arise from non-specific effects of brain damage. For example, striking out during caregiving, acute nocturnal confusion, and excessively loud vocalization when confronted by cognitive limitations might be understood as the result of unsophisticated caregiving, acute delirium, or catastrophic reaction. The above issues have hampered the NPS field's ability to agree on how to evaluate, differentiate, and treat NPS. Gaining consensus on a common algorithmic approach to evaluation, differentiation, and how and when to initiate non-pharmacologic psychosocial treatments, would lay solid foundation for tackling NPS in the clinical world, and inform research in developing new therapies. We present an Expert Consensus Panel's proposed unified algorithm for the assessment, differentiation, and treatment of NPS in AD. Three talks are envisioned, followed by a panel discussion. The first talk uses epidemiologic findings from several international studies to define the challenge posed by NPS overlap, varying etiologies, and differences by AD stage, and lays the conceptual background for the proposed algorithm. The second talk expands the Four "D's" systematic approach to evaluation and differentiation (Rabins, Lyketsos, and Steele, 1999) that allows clinicians and researchers to develop patient specific interventions. The final talk presents evidence supporting the use of psychosocial interventions for NPS linked to the outcomes of the "4D" method, and discusses both specific and non-specific psychosocial approaches to the management of individual NPS syndromes. The latter assumes that such well articulated psychosocial approaches must be used prior to medication treatments. The panel concludes with speaker and audience discussion moderated by the panel chair.

**F1-01-03 THE 4-D APPROACH TO MANAGING
NEUROPSYCHIATRIC SYMPTOMS**

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Background: In real-world settings, few treatment options are currently available for neuropsychiatric symptoms (NPS) with the exception of common (and often off-label) use of psychotropic medications. While behavioral management strategies have been repeatedly shown to have significant benefits without the physical risks of medications, such strategies have received limited use in clinical settings. This talk will articulate a systematic approach to the evaluation and differentiation of NPS resulting from a Fall 2010 Expert Consensus Panel. This approach, expands upon the Four "Ds" (Rabins, Lyketsos, and Steele, 1999), and includes four stages: 1) Describe; 2) Decode; 3) Devise and; 4) Determine. First (Describe stage), the provider works with the caregiver to place the problem behavior into context. In the Decode stage, possible causes of the problem behavior are investigated. Next, (Devise stage), the provider creates a tailored treatment plan incorporating patient/caregiver preferences; this includes concurrently treating physical problems found via Decode and emphasizing a first-line use of behavioral strategies. In the final Determine stage, the provider and caregiver later assess the efficacy of Devise interventions. The talk will further detail how use of this systematic approach enables the creation of simple and effective behavioral interventions tailored to the patient, caregiver and environmental context.

**FEATURED RESEARCH SESSIONS: F1-02
FEATURES OF STRUCTURAL AND FUNCTIONAL
CONNECTIVITY IN NORMAL AGING**

**F1-02-01 THE INFLUENCE OF COGNITIVE RESERVE ON
INTER-INDIVIDUAL VARIABILITY IN
RESTING-STATE CEREBRAL METABOLISM IN
NORMAL AGING**

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Background: There is a great deal of heterogeneity in the impact of aging on cognition and cerebral functioning. One potential factor contributing to individual differences among the elders is cognitive reserve which designates the partial protection from the deleterious effects of aging that lifetime experience provides. Neuroimaging studies examining task-related activation in elderly people suggested that cognitive reserve takes the form of more efficient use of brain networks and/or greater ability to recruit alternative networks to compensate for age-related cerebral changes. **Methods:** The current study examined the relationships between cognitive reserve, as measured by education and verbal intelligence, and cerebral metabolism at rest (FDG-PET) in a sample of 74 older participants. **Results:** Higher degree of education and verbal intelligence was associated with lower metabolic activity in the right posterior temporoparietal cortex and the left anterior intraparietal sulcus. Functional connectivity analyses of resting-state fMRI images in a subset of 41 participants indicated that these regions belong to the default mode network and a frontoparietal network respectively.

F1-02-02 STRUCTURAL CONNECTIVITY AS A SIGNATURE OF COGNITIVE AGING

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Methods: We compared age-sensitive cognitive functions, learning abilities, impulse control, and patterns of structural connectivity (DTI) between three groups of 65 cognitively normal subjects (20-40 years, 60-70 years, 71-85 years).

F1-02-03 STRUCTURAL CONNECTIVITY IN HEALTHY AGING: RELATION TO VISUOMOTOR FUNCTION AND COGNITION

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Background: Healthy aging is accompanied by compromise in brain white matter fiber integrity that is more pronounced in anterior than posterior and in superior than inferior fiber systems. To study the functional ramifications of degraded and intact structural connectivity in aging we used behavioral testing of interhemispheric function in combination with diffusion tensor imaging (DTI). **Methods:** Here, we focused on callosal fibers structurally connecting the two cerebral hemispheres and pontine fibers connecting the two cerebral hemispheres with the cerebellum. Quantitative analysis used our novel DTI-based fiber tract-driven topographical mapping to measure structure-function relations at specific locations within fiber tracts. **Results:** In healthy older adults, we found callosal fiber compromise that was most pronounced in anterior genu regions. In young adults, faster interhemispheric visuomotor transfer time was correlated with greater fiber integrity in the genu. By contrast, faster interhemispheric visuomotor transfer time was best predicted by greater fiber integrity in medial

callosal body regions in older adults. Although pons fiber integrity did not differ between young and older adults, greater integrity of anterior pontine fibers branching into the right cerebellar cortex were related to faster bilateral than unilateral visuomotor processing speed in older adults only, supporting a role for the pons in interhemispheric facilitation.

F1-02-04 CONNECTIVITY WITHIN THE DEFAULT MODE NETWORK IS RELATED TO WORKING MEMORY PERFORMANCE IN YOUNG BUT NOT ELDERLY HEALTHY ADULTS

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Results: Our data indicate that working memory performance is related to connectivity within the DMN in young healthy adults. The lack of such association in the elderly group suggests that DMN connectivity is not a determinant of memory function in normal aging. Instead, local processes, such as synaptic dysfunction, atrophy, abeta accumulation and microangiopathy might play a dominating role here.

FEATURED RESEARCH SESSIONS: F1-03 PHYSICAL ACTIVITY TO PROMOTE COGNITIVE FUNCTION

F1-03-01 THE INFLUENCE OF AN AEROBIC EXERCISE INTERVENTION ON BRAIN VOLUME IN LATE ADULTHOOD

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Background: There is growing interest in lifestyle factors and interventions that enhance the cognitive vitality of older adults and reduce the risk for cognitive impairment. Aerobic exercise is a promising method for enhancing cognitive and brain health throughout the lifespan. However, very little is understood regarding the molecular processes in humans that contribute to enhanced brain health with exercise or the impact that greater brain volume has on cognitive function. **Methods:** One-hundred twenty older adults without dementia were randomized to a moderate intensity walking group or to a stretching-toning control group for one-year. Magnetic resonance imaging (MRI) was used to assess cortical and hippocampal volume both before and after the intervention. Serum was obtained to assess concentrations of brain-derived neurotrophic factor (BDNF) and a cognitive battery was conducted before and after the intervention. **Results:** One year of aerobic exercise training increased the size of the anterior hippocampus by 2% in the exercise group as compared to the stretching-toning control group. These changes in hippocampal volume were positively correlated with changes in serum levels of BDNF. In addition, higher cardiorespiratory fitness was associated with greater volume of the prefrontal cortex, which mediated the link between fitness and cognitive performance. **Conclusions:** Overall, these findings suggest that the aging brain remains modifiable and that older adults who have been sedentary for at least 6-months can still benefit from starting a moderate walking regimen. Increases in hippocampal and prefrontal cortex volume are linked to improved cognitive function and increased levels of serum BDNF.